Table IV. % of Total Body Weight 24 Hr after the 16th Dose

	Liver	Testes	Vesicular glands	Vas Deferens and epididymis
Control	4.35 ± 0.19	1.09 ± 0.05	0.12 ± 0.02	0.22 ± 0.02
2	4.46 ± 0.11	1.06 ± 0.02	0.13 ± 0.01	0.24 ± 0.01
3	4.19 ± 0.41	1.13 ± 0.10	0.12 ± 0.06	0.31 ± 0.10
4	4.22 ± 0.38	1.05 ± 0.09	0.06 ± 0.02	0.20 ± 0.11
6	4.51 ± 0.15	1.23 ± 0.12	0.11 ± 0.04	0.23 ± 0.05

Table V. Estrogenic Activity in Ovariectomized Sprague–Dawley Rats

	N	% control of uterine wt	p
Control (1% CMC)	21	100 ± 23	
1	13	260 ± 22	0.001
2	8	72 ± 16	n.s.
3	8	131 ± 20	0.050
4	8	195 ± 19	0.001
6	8	74 ± 17	n.s.
Ethinylestradiol	8	259 ± 9	0.001

The propensity of the benzene ring to undergo bioactivation *via* hydroxylation[7] and the effect some hydroxylated aromatic compounds (*e.g.*, diethylstilbestrol) have upon the reproductive cycle led to the speculation that the uterotropic or antifertility activities might be the result of *in vivo* hydroxylation. Conversely, a substituent (*e.g.*, fluorine) which forms a more stable bond with the ring than does hydrogen would be expected to interfere with bioactivation and lower the antifertility activity of the compound.[8,9]

The *p*-fluoro derivative **4** retained both hypocholesterolemic and uterotropic activities and showed a marked drop in antifertility effect compared to the parent compound. The *o*-fluoro analog has an antifertility effect as great as dibenzylcyclooctanone. These compounds support the concept that para hydroxylation may be responsible for the antifertility effect of dibenzylcyclooctanone at the tissue level.

Both *o*- and *p*-hydroxy derivatives were inactive when tested, even if administered ip rather than by the usual oral route. Since the compounds are phenols, it is conceivable that either the lipid solubility had been severely altered or that nonspecific binding to protein or other macromolecules was preventing delivery to the active site. Esterification of the para derivative with acetic acid **6** led to the recovery of antifertility activity without uterotropic or hypolipidemic (serum cholesterol and triglyceride) effect. Furthermore, there was no change in lipid, protein, or glycogen content of the liver with **6** which is contrary to the effects of the parent.[2] Esterification of the *o*-hydroxy derivative led to a compound too unstable to characterize or test reliably, although spectral evidence indicated that the product initially obtained was an ester. Preliminary screening showed activities similar to **6**. Those compounds which demonstrated hypocholesterolemic activity (**2**, 3, and 4) caused no deposition of lipids in the liver and **2**, **3**, and **6** caused no atrophy of the vesicular gland or vas deferens and epididymis contrary to the parent compound (Table IV).

Thus with compound **6** we feel that the antifertility activity has successfully been separated from the uterotropic and hypocholesterolemic activities. Furthermore, since compound **6** has no uterotropic activity then this compound cannot be inhibiting pregnancy at this dose due to its estrogenic characteristics and, thus, its mechanism of action must be elsewhere, a theory that we have previously advanced with regard to the antifertility activity of the 2,8-dibenzylcyclooctanone series.[1]

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Homologs of Dopa, α-Methyldopa, and Dopamine as Potential Cardiovascular Drugs

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Starting from 3,4-dimethoxyphenacyl bromide, 2-amino-4-(3,4-dihydroxyphenyl)butyric acid (homodopa) was synthesized in six steps. 5-Hydroxyhomodopa was similarly prepared. α-Methylhomodopa was synthesized in four steps from zingerone [4-(4-hydroxy-3-methoxyphenyl)-2-butanone]. α-Methylhomodopa showed no antihypertensive activity in the genetic hypertensive rat. Homodopa did not potentiate the behavioral effect of Dopa or inhibit Dopa decarboxylase. Homodopamine, unlike dopamine, did not increase renal blood flow in the dog.

Recent interest in biogenic amines and amino acids has been highlighted by the introduction of Dopa and α-methyldopa as anti-Parkinson and antihypertensive agents, respectively. Many substituted Dopa and tyrosine analogs have been made, the most recent being tetralin and indan analogs.[1] However, no one has reported on homologs of Dopa or α-methyldopa. The closest example is the homolog of tyrosine reported by Evans and Walker.[2] The homolog of dopamine has only been mentioned once[3] in the literature with no method of preparation given, and it was stated that it had "⅔ of the pressor action of dopamine."

A mechanism of action of α-methyldopa was proposed by

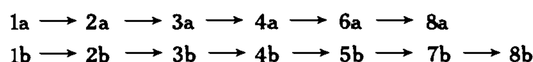
which blood pressure is lowered *via* a central α-adrenergic stimulation by its metabolite α-methylnorepinephrine.[4] It was hoped that homodopa and homo-α-methyldopa would act in a like manner. Structurally these homologs have similar extended O–N distances to the natural amino acid 5-hydroxytryptophan (5-HTP), and 5-HTP has been reported to lower blood pressure by a peripheral[5] and a central[6] mechanism.

Since α-methyldopa shows Dopa decarboxylase inhibition, our compounds were also evaluated for activity *vs.* this enzyme.

We also synthesized 5-hydroxyhomodopa **8b** and keto analogs **6a** and **6b** for evaluation. The amines corresponding to homodopa and homo-α-methyldopa, **17a** and **15**, were synthesized to determine if the amino acids decarboxylated and to compare their activity to dopamine.

Chemistry. α-Bromo-3,4,5-trimethoxyacetophenone (**1**) has been converted to the *N*-acetylamino acid **4a** by Horton and Thomson.[6] This compound was demethylated and deacetylated to **6a,** and then the keto group was reduced to the target 5-hydroxyhomodopa **8a**. Using Horton's procedure, **4b** was prepared from **1b.** In this series the ketone was reduced first and then the methoxy and acetyl groups were removed to give homodopa **8b** (Scheme I).

Scheme I



α-Methylhomodopa (**13**) was prepared in four steps from commercially available zingerone (**9**) as outlined in Scheme II. Zingerone was also used to prepare α-methylhomodopamine (**15**) (Scheme III).

Scheme II

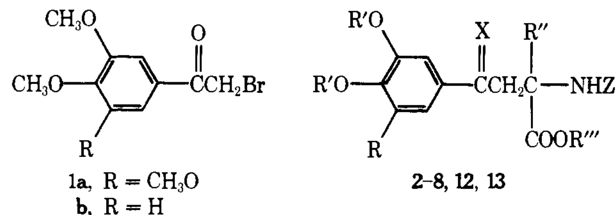
Scheme III

Homodopamine (**17a**) and its 2,3 isomer **17b** were prepared from the known amides **16a** and **16b** (Scheme III). We wished to evaluate **17b** because its N to ortho O distance is similar to dopamine itself.

Pharmacology. These compounds were evaluated as antihypertensives in the normotensive and the genetic hypertensive rat. In the normotensive rat neither the amino acids (**6a,b, 8a,b,** or **13**) nor the amines (**15, 17a,b**) showed a significant decrease in blood pressure at an ip dose of 30 mg/kg. In the genetic hypertensive rat, α-methylhomodopa (**13**) did not show any antihypertensive activity at the ip dose of 200 mg/kg, a dose where α-methyldopa was quite active. The amines (**17a,b** and **15**) were tested for possible stimulation of renal blood flow in the anesthetized dog. None did so at a dose of 1.0 mg/kg iv, in contrast to dopamine which at 0.030 mg/kg iv increased renal blood flow by 85% in 5 min.

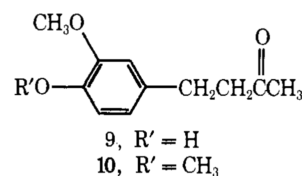
Because of the structural similarity to Dopa and dopamine, these compounds were tested for inhibition in two enzyme systems—Dopa decarboxylase and dopamine β-hydroxylase. The only significant activity was for homodopamine (**17a**) which showed a 56% inhibition of dopamine β-hydroxylase at 3×10^{-4} *M*.

These compounds were evaluated for potentiation of Dopa-induced behavior by the method or Everett.[7] Only 5-hydroxyhomodopa (**8a**) showed marked potentiation at

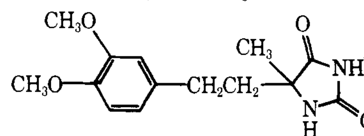


1a, R = CH_3O
b, R = H

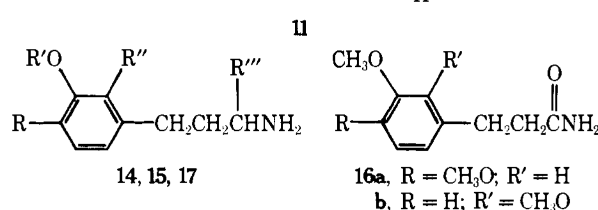
2–8, 12, 13



9, R′ = H
10, R′ = CH_3



11



14, 15, 17

16a, R = CH_3O; R′ = H
b, R = H; R′ = CH_3O

No.	R	R′	R″	R‴	X	Z
2a	CH_3O	CH_3	COOEt	Et	O	$COCH_3$
2b	H	CH_3	COOEt	Et	O	$COCH_3$
3a	CH_3O	CH_3	COOH	H	O	$COCH_3$
3b	H	CH_3	COOH	H	O	$COCH_3$
4a	CH_3O	CH_3	H	H	O	H
4b	H	CH_3	H	H	O	H
5b	H	CH_3	H	H	H_2	H
6a	HO	H	H	H	O	H
6b	H	H	H	H	O	H
7b	H	CH_3	H	H	H_2	H
8a	HO	H	H	H	H_2	H
8b	H	H	H	H	H_2	H
12	H	CH_3	CH_3	H	H_2	H
13	H	H	CH_3	H	H_2	H
14	HO	CH_3	H	CH_3		
15	HO	H	H	CH_3		
17a	HO	H	H	CH_3		
17b	H	H	HO	H		

25 mg/kg oral dose. A similar test using 5-hydroxytryptophan (5-HTP) instead of Dopa has been developed at our laboratories by N. Plotnikoff. Since the O–N distance in our compounds is similar to that in 5-HTP, we thought they might have 5-HTP like properties. However, none of these compounds was found to potentiate 5-HTP induced behavior.

No evidence for decarboxylation of homodopa or α-methylhomodopa to their respective amines **17a** or **15** was observed in the brains and hearts of rats. See Experimental Section for details.

Discussion

To show hypotensive activity, α-methylhomodopa would have to release α-methylhomodopamine into the brain, and α-methylhomodopamine once in the brain would have to exert a central hypotensive action as does α-methylnorepinephrine. Since we show that α-methyldopa is not decarboxylated, α-methylhomodopamine is never formed. When this amine is administered ip, it, in all probability, never crosses the blood brain barrier and so is inactive. One would have to infuse α-methylhomodopamine into brain

ventricles (as Heise and Kroneberg[17] did for α-methyldopamine and α-methylnorepinephrine) to determine if α-methylhomodopamine had hypotensive activity if delivered to the site of action.

Experimental Section

All new compounds gave satisfactory elemental analyses (±0.4%). Nmr and ir spectra were in full accord with the proposed structures. Melting points were uncorrected.

2-Amino-4-keto-4-(3,4,5-trimethoxyphenyl)butyric Acid (6a). The trimethoxy compound **4a**[6] (9.00 g, 27.7 mmol) was refluxed in 100 ml of 48% HBr under N_2 atmosphere for 5 hr. The solution was concentrated *in vacuo* leaving a dark powder. This was dissolved in 140 ml of water, made slightly basic with diethylamine, and then made slightly acidic with acetic acid (pH 6). The solution was cooled in an ice bath and filtered to give 6.8 g (100%) of **6a** after drying in a vacuum oven at 80°: mp >250°; negative $AgNO_3$ test for Br. *Anal.* ($C_{10}H_{11}NO_6$) C, H, N.

2-Amino-4-(3,4,5-trihydroxyphenyl)butyric Acid Acetate (8a). Acetic acid (200 ml), **6a** (1.50 g, 6.20 mmol), and 5% Pd/C (1.0 g) were hydrogenated at 3 atm at 50°. The catalyst was removed and the solution concentrated *in vacuo*. The residue was crystallized (H_2O–Me_2CO) giving 0.70 g (39%) of **8a** acetate, mp 130–132°. It gave a positive ninhydrin test. *Anal.* ($C_{10}H_{13}NO_5 \cdot C_2H_4O_2$) C, H, N.

Diethyl Acetylamino(3,4-dimethoxyphenyl)malonate (2b). 3,4-Dimethoxyphenacyl bromide[8] (83.2 g, 0.322 mol) was allowed to react with 74.2 g (0.341 mol) of diethyl acetylaminomalonate, 14.3 g (0.341 mol) of 57% NaH, 1.5 l. of dry benzene, and 23 ml of EtOH by the same procedure used to prepare **2a**.[2] There was obtained 106.9 g (84%) of **2b**, mp 132–135° (from EtOH). *Anal.* ($C_{19}H_{25}NO_8$) C, H, N.

Acetylamino(3,4-dimethoxyphenacyl)malonic Acid (3b) and 2-Acetylamino-4-keto-4-(3,4-dimethoxyphenyl)butyric Acid (4b). By the procedure used to prepare **4a**,[6] the above ester **2b** (95.5 g, 0.242 mol) was converted into 72.8 g (89%) of **3b**, mp 150–153°, and then into 45.5 g (72%) of **4b**, mp 198–200°. *Anal.* ($C_{14}H_{17}NO_6$) C, H, N.

2-Acetylamino-4-(3,4-dimethoxyphenyl)butyric Acid (5b). Acetic acid (250 ml), **4b** (15.0 g, 51.0 mmol), and 5% Pd/C (5.0 g) were hydrogenated at 3 atm at 50°. The catalyst was removed, the solvents were concentrated *in vacuo*, water was added, and the solution was concentrated again *in vacuo*. The residue was crystallized twice from water giving 10.0 g (70%) of **5b**, mp 129–130°. *Anal.* ($C_{14}H_{19}NO_5$) C, H, N.

2-Amino-4-(3,4-dimethoxyphenyl)butyric Acid (7b). The above amide **5b** (7.10 g, 25.3 mmol) was refluxed 1 hr in 38 ml of 3 *N* HCl. The solution was concentrated *in vacuo* and cooled giving crystals which were recrystallized (*i*-PrOH) to give 5.50 g (78%) of **7b**, mp 199–201°. *Anal.* ($C_{12}H_{17}NO_4 \cdot HCl$) C, H, N.

2-Amino-4-(3,4-dihydroxyphenyl)butyric Acid (8b). The above amine **7b** (12.8 g, 4.66 mmol) was dissolved in 200 ml of HOAc and 39 g of 48% HBr. The solution was saturated with HBr gas, heated at 125° for 4.5 hr, and then concentrated *in vacuo*. Water was added and the solution concentrated to dryness. The residue was dissolved in acetone and the solution made slightly basic with diethylamine. The oil which formed was crystallized (H_2O–Me_2CO) to give 7.0 g (71%) of **8b**, mp 254–257°. *Anal.* ($C_{10}H_{13}NO_4$) C, H, N. The hydrochloride had mp 197–200° (crystallized from *i*-PrOH).

2-Amino-4-keto(3,4-dihydroxyphenyl)butyric Acid (6b). The amide **4b** (4.0 g, 13.5 mmol) was converted to **6b** by the same procedure as for the preparation of **6a**: yield 2.90 g (95%) of **6b**; mp 258°. *Anal.* ($C_{10}H_{11}NO_5$) C, H, N.

4-(3,4-Dimethoxyphenyl)-2-butanone (10). Zingerone (**9**) (Aldrich Chemical Co.) (9.00 g, 4.95 mmol), 7.15 g (56.7 mmol) of dimethyl sulfate, 7.85 g (56.7 mmol) of powdered K_2CO_3, and 75 ml of acetone were refluxed 16 hr. The solution was cooled, filtered, and concentrated, and the resulting oil was treated with 25% KOH. A solid formed, which was crystallized (Et_2O–hexane) to give 7.4 g (76%) of **10**, mp 55–56° (lit.[9] mp 53–56°).

5-(3,4-Dimethoxyphenethyl)-5-methylhydantoin (11). Ketone **10** (35.4 g, 0.180 mol), $(NH_4)_2CO_3$ (148 g, 1.5 mmol), and 15.5 g (0.239 mol) of KCN were dissolved in 1.10 l. of 50% EtOH and heated at 60° for 8 hr. The solution was concentrated *in vacuo* to 500 ml and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated to give 41.9 g (83%) of 11: crystallized from EtOAc–ether; mp 130–132°. *Anal.* ($C_{14}H_{18}N_2O_4$) C, H, N.

2-Amino-4-(3,4-dimethoxyphenyl)-2-methylbutyric Acid (12). Hydantoin **11** (3.72 g, 13.3 mmol) was treated with 8.0 g of $Ba(OH)_2$ in 100 ml of water at 165° in an autoclave. After 45 min the solution was cooled, acidified with 6 *N* H_2SO_4 (25 ml), and filtered through hyflo-supercel. The filtrate was made basic (pH 8) with diethylamine, then acidic (pH 6) with HOAc, concentrated to about one-third, and cooled to give 2.0 g (63%) of **12**, mp 222–224° (crystallized H_2O). *Anal.* ($C_{13}H_{19}NO_4$) C, H, N.

2-Amino-4-(3,4-dihydroxyphenyl)-2-methylbutyric Acid (13). By the procedure for conversion of **7b** to **8b**, 15.0 g (62.1 mmol) of **12** was converted to 8.5 g (61%) of **13**, mp 254–260° (crystallized from H_2O + a few drops of HOAc). *Anal.* ($C_{11}H_{15}NO_4$) C, H, N. An HCl salt was prepared: mp 187–190°.

3-(3,4-Dihydroxyphenyl)propylamine (Homodopamine) Hydrobromide (17a). 3-(3,4-Dimethoxyphenyl)propylamine (5.0 g, 25.6 mmol), prepared from amide **16a**,[10] in 20 ml of HOAc was added to a solution of 20 g of 48% HBr and 100 ml of HOAc, saturated with HBr gas at 25°. The resulting solution was heated at 125° for 5 hr. The solvent was concentrated *in vacuo*, water was added, and the solution was concentrated again. Benzene was added and the result concentrated once more. The residue was crystallized (*i*-PrOH) to give 5.40 g (89%) of **17a**, mp 156–158°. *Anal.* ($C_9H_{13}NO_2 \cdot HBr$) C, H, N.

4-(3,4-Dihydroxyphenyl)-2-butylamine Hydrobromide (15). Zingerone (**9**) was converted to **14** as described in the literature.[11] The hydrochloride of **14** (10.0 g) was converted to **15** in a manner similar to that of **17a**. The product HBr salt was a noncrystalline colorless glass. Its nmr spectrum showed the absence of CH_3O: nmr (in D_2O) δ 1.47 (3 H, d), 2.00 (2 H, m), 2.63 (2 H, t), 3.47 (1 H, m), 6.75 (1 H, q, J = 8, J = 2 Hz), 7.00 (1 H, d, J = 2 Hz), 7.07 (1 H, d, J = 8 Hz).

3-(2,3-Dihydroxyphenyl)propylamine Hydrobromide (17b). 3-(2,3-Dimethoxyphenyl)propionamide[12] (**16b**) was reduced with $LiAlH_4$ to 3-(2,3-dimethoxyphenyl)propylamine as in the preparation of **16a**.[10] The dimethoxy compound (12.3 g, 63.0 mmol) was treated with HBr–HOAc–H_2O as above giving 13.5 g (86%) of **17b**, mp 141–143°, crystallized from *i*-PrOH–C_6H_6. *Anal.* ($C_9H_{13}NO_2 \cdot HBr$) C, H, N.

Pharmacology. Enzyme Inhibition Assay. Dopa decarboxylase assay was done by the method of Schales.[13] Dopamine β-hydroxylase was determined by a radio assay modification[14] of the method of Friedman and Kaufman.[15]

Dopa potentiation is described by Everett.[7] **5-Hydroxytryptophan potentiation.** Three mice are first pretreated with pargyline (40 mg/kg ip), followed by the drug (oral), and then challenged with 5-HTP 4 hr later. Effects observed are tremors, head movements, abducted limbs, and irritability.

The blood pressure of conscious, restrained, genetically hypertensive rats was measured directly *via* a cannulated caudal artery and/or indirectly using an occluding cuff on the tail.

Renal Blood Flow. An anesthetized dog with an electromagnetic flow probe placed around the renal artery was catheterized for measurement of arterial blood pressure, left ventricular systolic pressure, and heart rate. Cannulas were also introduced for intravenous and intraduodenal administration of drugs.

Rat Study for Possible Decarboxylation. The amino acids **8b** and **13** were administered ip to male rats (Long-Evans) at 200 mg/kg. Three hours later the brains and hearts were removed and extracted with 0.4 *M* $HClO_4$. These extracts were neutralized and analyzed by a column chromatographic method[16] which separated into individual peaks, norepinephrine, dopamine, **15**, and **17a**. Neither **15** nor **17a** was found in these animals.

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N-Cyclopropyltryptamines, Potent Monoamine Oxidase Inhibitors

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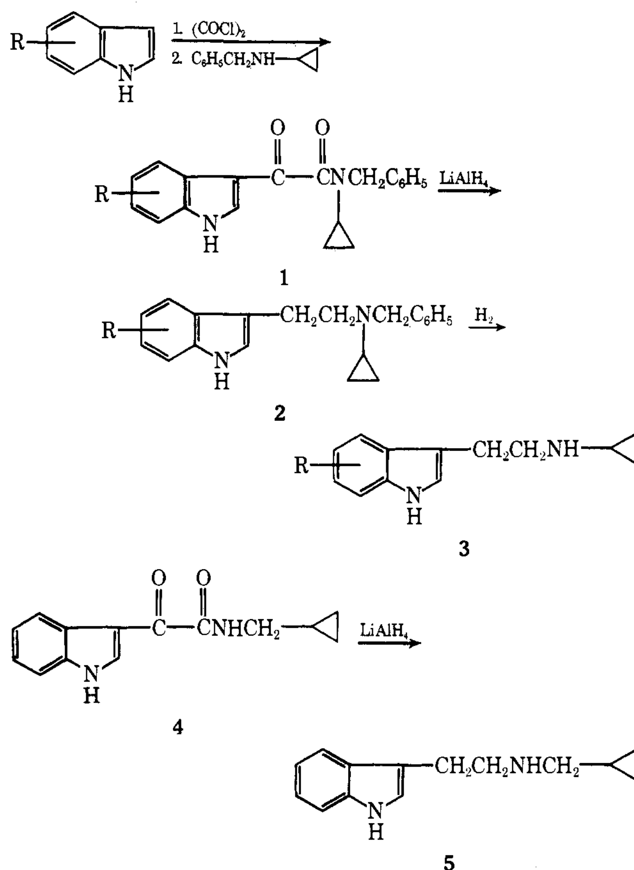
N-Cyclopropyltryptamine as well as the 5- and 7-methoxy derivatives is a potent monoamine oxidase inhibitor for both tyramine and tryptamine substrates.

The use of monoamine oxidase inhibitors as antidepressants has been largely replaced by the tricyclic antidepressants because of the hypotensive side effect of the MAO inhibitors. This field has been recently reviewed by Ho.[1] The most interesting recent developments have been the MAO inhibitors which have been reported to have selective action for tryptamine or serotonin over tyramine. Some examples are (phenoxyethyl)cyclopropylamine,[2] clorgyline,[3] and *N*-methyl-*N*-propargylamphetamine.[4] Certain tryptamines and certain cyclopropylamines have MAO inhibitory action,[1] but cyclopropyltryptamines have not yet been reported in the literature. In an attempt to get a MAO inhibitor specific for serotonin and tryptamine, we prepared three *N*-cyclopropyltryptamines (unsubstituted, 5-CH_3O, and 7-CH_3O) and *N*-cyclopropylmethyltryptamine. We synthesized the 7-CH_3O compound because of the work of Ho[5] on carbolines, in which substituents in the equivalent position enhance MAO inhibitory activity.

The compounds were prepared by a straightforward synthesis outlined in Scheme I. Attempted preparation of the 7-chloro analog of **3** failed when dechlorination accompanied debenzylation in the last step. A benzyl-protecting group is necessary because cyclopropylamides with free NH undergo ring opening on reduction with $LiAlH_4$.[10]

Scheme I



a, R = H; **b**, R = 5-OCH_3; **c**, R = 7-OCH_3

Pharmacology. Only structure **3** showed MAO inhibitory properties. The most potent was the unsubstituted compound **3a**, which was even more potent than pargyline. However, **3a** was equally potent with tyramine as a substrate as it was for tryptamine, so the hoped for selectivity was not present (Table I).

These compounds were tested for potentiation of the behavioral effects of 5-hydroxytryptophan (5-HTP) in mice. This test is similar to the Dopa potentiation test.[6] See Experimental Section for details. Compound **3a** showed marked potentiation of 5-HTP at 10, 25, and 100 mg/kg orally. Compound **3c** showed marked potentiation of 5-HTP at 10, 25, and 100 mg/kg and moderate potentiation at 5 mg/kg. However, **3b**, the compound which is the closest analog of serotonin, did not potentiate 5-HTP even at 100 mg/kg.

Mouse symptomatology for these compounds showed tremors, decreased motor activity, ataxia, and dilation of blood vessels at 10 mg/kg oral dose for **3a** and **3b** (dilation of blood vessels occurs at 1.0 mg/kg for **3b**). Compound **3c** did not show tremors or decreased motor activity until 100 mg/kg (oral dose) with no dilation of blood vessels. This vasodilation was noted as a reddening of the ears of the mice. The cyclopropylmethylaminotryptamine (**5**) showed little, if any, observable effects. Oral LD_{50}'s for **3a–c** and **5** respectively were 100, 100, 750, and 750 mg/kg (animals observed for 24 hr).

Experimental Section

All new compounds gave satisfactory elemental analyses (±0.4%). Nmr and ir spectra were in full accord with the assigned structure. Melting points were uncorrected. Concentrations *in vacuo* were done on a Büchi rotovac.

***N*-Benzyl-*N*-cyclopropylindole-3-glyoxalamide (1a).** Oxalyl chloride (25 g, 0.197 mol) in 80 ml of ether was added dropwise to 20.0 g (0.17 mol) of indole in 300 ml of ether at 0°. After stirring 20